Tibia lead, folate, MTHFR genotype, and birth weight.

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Maternal folate intake/status and birth weight

- Maternal folate intake or status are associated with fetal and birth outcomes—birth weight, intrauterine growth retardation.
- Folate status seems to explain a small portion of the variability in birth weight.

Folate-gene interactions

- Folate—is a substrate for methylenetetrahydrofolate reductase (MTHFR), which participates in one-carbon metabolism.
- Polymorphisms of the *MTHFR* gene (C → T substitution at nucleotide 677) are fairly common, depending on geographic region.
  - Frequency of homozygous individuals as high as 36% in Mexican populations
- Certain *MTHFR* genotypes produce enzymes with lower metabolic activity.

MTHFR, folate, and size at birth

- The effects of folate are particularly evident in women with certain polymorphisms in genes responsible for folate metabolism.
  - Maternal *677TT* genotype paired with low RBC folate, was associated with lower birth weights.
  - But, maternal MTHFR variants (*1298CC* and *677TT*) not associated with negative outcomes, even in women who had low (500 µg/day) second-trimester folate intakes.

Lead exposure and birth weight

- Lead exposure during fetal development has also been associated with lower birth weight and small for gestational age births in some studies.
- The magnitude of these effects has been modest and comparable to the effects of nutritional deficiencies.
  - In Mexico women, 7.3 g decrease in BW for every 1 µg/g increase in bone lead.
- No studies of metabolic links specifically between lead and folate, or *MTHFR.*

Objectives

- Do maternal *MTHFR* polymorphisms modify the relationship between maternal folate intake and birth weight or between fetal lead exposure and birth weight?

Design and methods

Study Overview

- Study period: January 1994 – June 1995
- Mexico City—3 hospitals serving low-to-middle income populations
- Women were approached when presenting to the hospital for delivery
  - Asked about willingness to participate in a randomized Ca supplementation trial 1 month after delivery

Data Collection

- Anthropometry, maternal and umbilical blood collection within 12 hours of delivery.
- Food intake determined with a semi-structured food frequency questionnaire (FFQ)
- Bone lead levels measured using a spot-source ^{109}Cd KXRF instrument at 1 month post-partum.
- *MTHFR* genotyping on archived blood samples
  - SNPs at loci 594, 677, and 1298 were examined.

Data Analysis

- For *MTHFR* SNPs, assumed dominant effects.
- Birth weight was modeled as a function of maternal folate intake, tibia lead, and *MTHFR* SNP.
- Analyses stratified by genotype:
  - Folate intake & tibia lead were fit into models predicting birth weight.
- Models adjusted for variables known to influence birth weight: maternal age, height, total years of schooling, marital status, post-partum MUAC, gestational age, parity, and sex of the child.

Results

Sample characteristics

	In Study (n=495)	Excluded (n=112)
Age (y)	24.5 ± 5.1	24.7 ± 5.4
Height (m)	1.54 ± 0.05	1.52 ± 0.05
Total schooling (y)	9.4 ± 3.2	8.7 ± 3.2
Years living in Mexico City	20.5 ± 8.3	20.7 ± 8.9
Tibia lead (μg/g)	9.9 ± 10.1	10.4 ± 10.4
% folate < 400 μg/d	35.3	36.0
% Primiparous	43.6	40.3
Gestational age (wk)	39.4 ± 1.2	39.2 ± 1.3
Birthweight (g)	3166 ± 417	3003 ± 412
Ever smoke (%)	43.4	46.6

MTHFR allele frequencies

594 C→T

	n
CC	448
CT	36
TT	1

Allele frequency

3.9%

677 C→T

	n
CC	68
CT	242
TT	152

Allele frequency

59.1%

1298 A→C

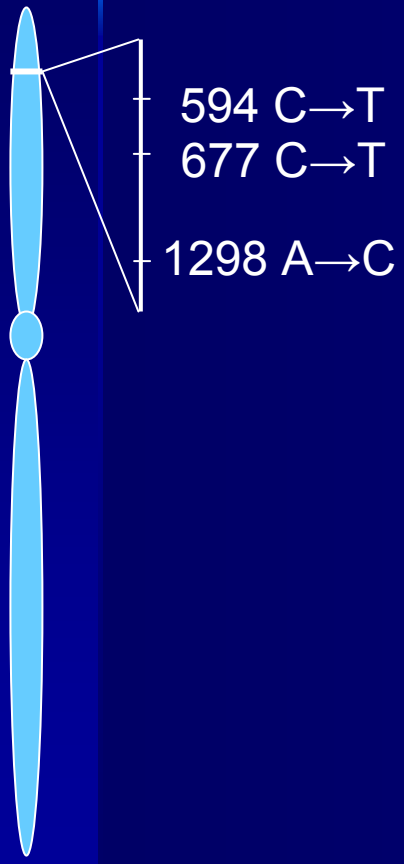
	n
CC	384
CT	87
TT	8

Allele frequency

10.7%

All variants in Hardy-Weinberg equilibrium.

MTHFR haplotypes



1	2	3	4
A	A	A	a
a	A	A	A
A	A	a	a
n=395	n=37	n=19	n=37

Dominant effect analysis

For SNPs

594 C→T

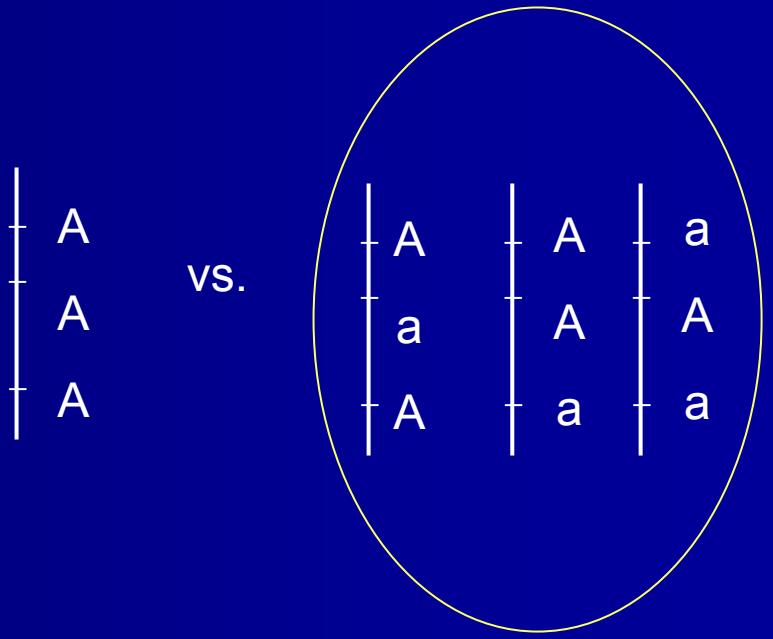
	n
CC	448
CT	36
TT	1

Wild type

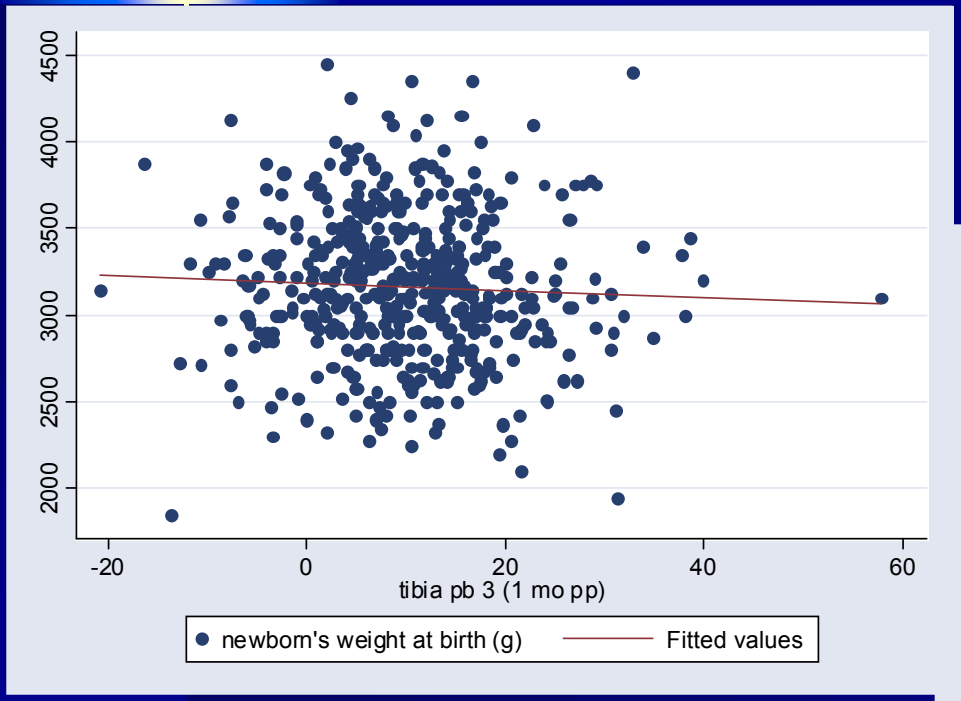
vs.

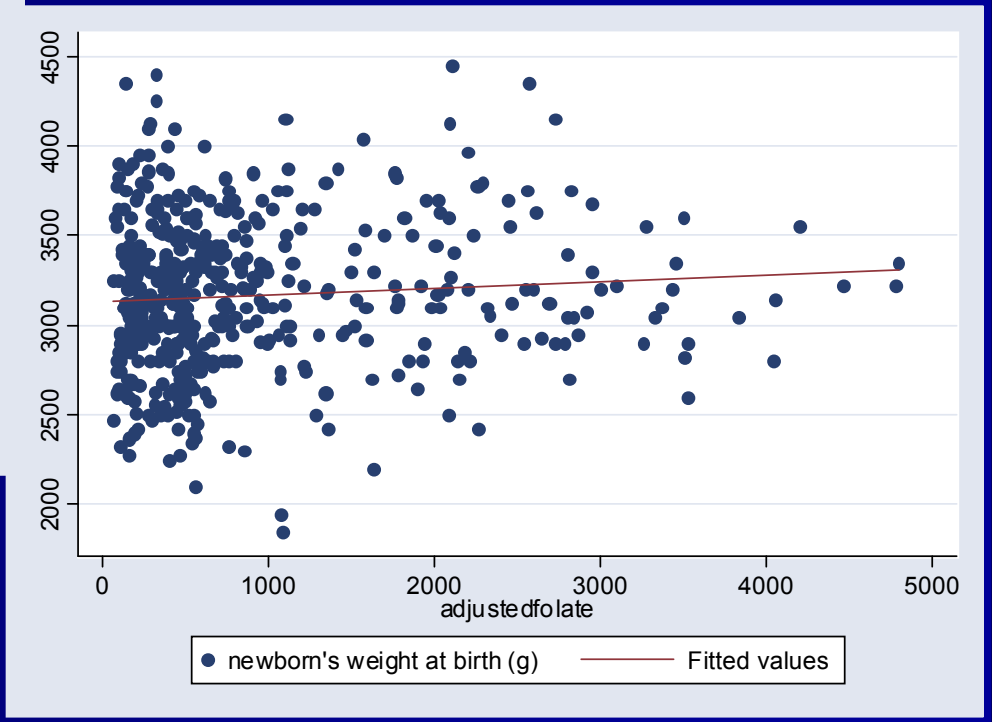
Carrier

For haplotypes



Birth weight vs. Tibia Lead and Folate Intake





Tibia lead, folate intake and BW

Predictor	N	Adjusted[2] β ± SE
Folate intake (µg/d)	495	0.04 ± 0.02**
Tibia lead (µg/g)	494[1]	-4.1 ± 1.8**

**p<0.05; [1]Tibia lead >70µg/g removed; [2]Adjusted for maternal age, total years of schooling, child sex, parity, marital status, gestational age, maternal height, postpartum arm circumference, smoking.

MTHFR genotypes and BW

Predictor	N	Adjusted[1] β ± SE
594 carrier	485	-42.1 ± 65.6
677 carrier	562	60.2 ± 50.1
1298 carrier	479	-34.9 ± 44.0
Haplotype[2]	487	104.9 ± 65.4

[1]Adjusted for maternal age, total years of schooling, child sex, parity, marital status, gestational age, maternal height, postpartum arm circumference, smoking. [2]Both haplotypes considered in this analysis.

Tibia, folate, and BW—by SNPs

Adjusted β ± SE

	C594T	C677T	A1298C
	Wild type		
N	447	68	383
Folate (µg/d)	0.03 ± 0.02	0.04 ± 0.05	0.02 ± 0.02
Lead (µg/g)	-5.6 ± 1.9***	-13.3 ± 6.0**	-6.6 ± 2.1***
	Carriers		
N	37	393	95
Folate (µg/d)	0.03 ± 0.09	0.04 ± 0.02*	0.09 ± 0.05*
Lead (µg/g)	21.2 ± 7.8**	-4.4 ± 2.0*	3.5 ± 3.8

***p<0.01, **p<0.05, *p<0.1; Adjusted for maternal age, total years of schooling, child sex, parity, marital status, gestational age, maternal height, postpartum arm circumference, smoking.

Tibia, folate, and BW—by haplotype[1]

	Wild Type n=37 Adjusted[1] β ± SE	Any Variants n=450 Adjusted β ± SE
Folate (µg/d)	-0.01 ± 0.07	0.05 ± 0.02**
Lead (µg/g)	-17.4 ± 10.4	-4.0 ± 1.8**

**p<0.05, *p<0.1; [1]Adjusted for maternal age, total years of schooling, child sex, parity, marital status, gestational age, maternal height, postpartum arm circumference, smoking. [2]Both haplotypes considered in this analysis.

Discussion

- Maternal lead exposure negatively associated with birth weight in Mexican newborns.
  - Birth weight was within "normal" range, with 4.4% of infants born LBW.
- Increased folate intake was positively associated with birth weight.
- *MTHFR* polymorphisms were not independently related to birth weight in this population.

Discussion

- Carrier status for any of the SNPs seemed protective against the effects of prenatal lead exposure on birth weight.
  - Women with lower MTHFR activity are not as affected as women with normal activity.
- Lead and other metals are related to changes in DNA methylation status.